REMARKS/ARGUMENTS

Claims 1-8 have been cancelled. Claims 9-17 have been added. Hence, claims 9-17 are currently under consideration.

Sequence Requirements

In the communication mailed December 28, 2005, the Examiner states that the specification fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825. In response, applicants request that the attached substitute sheets containing a substitute Sequence Listing, which includes the sequences listed on pages 4-5, 7, 11 and 15 of the specification and identified as SEQ ID NO. 8, SEQ ID NO. 26, SEQ ID NO. 27, SEQ ID NO. 28 and SEQ ID NO. 29. The applicant has also amended the header information to properly identify the continuity data for the application. The substitute Sequence Listing is supported by the application as originally filed and does not include any new matter. Also included herewith is a diskette containing the substitute Sequence Listing in computer readable form (CRF). Pursuant to 37 C.F.R. 1.821(f), the undersigned states that the substitute Sequence Listing content of the paper copy and the computer readable form (CRF) contained on the diskette is identical.

In view of the foregoing submissions and amendments to the instant application, Applicants submit that the requirements under 37 C.F.R. §§1.821-1.825 have been met and the Notice to Comply has been completely addressed.

The specification is also amended as set forth hereinabove indicating the respective SEQ ID NOS. following each sequence.

In the communication mailed December 28, 2005, the Examiner has rejected claims 1 and 3-6.

Claim Rejections – 35 USC § 101

Claim 1 has been rejected under 35 U.S.C. § 101 as being allegedly non-statutory subject matter. In response, applicants have introduced the limitation "isolated" into the new claims and maintain that the rejection is now moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections – 35 USC § 112, second paragraph

Claims 1 and 3-6 have been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. According to the Office Action, it is unclear where the numeric number of the first amino acid residue starts. In response, applicants have cancelled claims 1-8 and have added new claims 9-17. New independent claim 9 specifically recites "wherein the amino acid is numerated from the beginning of the coding region of I377/NS2-3' construct (EMBL genebank accession number No. AJ 242651)." Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections – 35 USC § 112, first paragraph

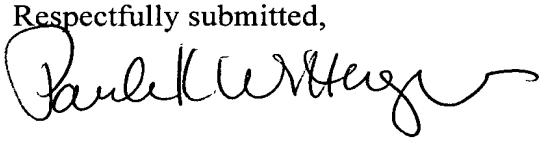
Claims 1 and 3-6 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Office Action, the specification does not reasonably enable one skilled in the art to make and use any or all HCV self-replicating polynucleotide having a mutation at the position 2042 from G to C or G to R. The Office Action indicates that there apparently is a concern regarding cytotoxicity to the host cell. In response, applicants have cancelled claims 1-8 and have added new claims 9-17. New independent claim 9 recites that the "HCV polyprotein that comprises: HCV NS3, NS4A, NS4B, NS5A, and NS5B polypeptides," and further requires an amino acid substitution of G to C or G to R at position 2042. Applicants first would like to note that one skilled in the art could readily build in the desired mutation by site-directed mutagenesis into any isolated HCV RNA molecule, but more particularly in the original RNA molecule I_{377}/NS2-3 (corresponding to APKG12) that is deposited as EBML Geneback accession number AJ242651. Once the mutation has been built in the desired HCV RNA molecule, such mutated RNA can be transfected in appropriate host cells, cultured and used to measure RNA replication in such cells. There is no requirement that the mutation be isolated *de novo* in order to reproduce the invention.

Applicants further submit that transfection of the RNA and its replication is NOT toxic to the cell because infectious viral particles are not produced from the replication. As is well recognized by the state of the art (and supported in the Review article of Bartenchlager & Lohman, J. Gen. Virol. (2000), **81**:1631-1648, which is enclosed for your convenience) the sequences of the structural proteins were deleted from the replicon

construct to avoid high expression levels of the structural proteins that constitute the viral particles (virions) which may be cytotoxic. Therefore, it is not the viral particles that are replicated in the host cells but only the transfected RNA molecule comprising the non-structural genes. In fact, cells have been stably transfected without impairing their growth ability. See e.g., Ali et al., "Hepatitis C Virus Subgenomic Replicons in the Human Embryonic Kidney 293 Cell Line" J. of Virology (2004) 78:491-501, which is enclosed for your convenience. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections.

In view of the foregoing, it is respectfully submitted that the subject application is in condition for allowance and such favorable action at an early date is earnestly solicited.

Respectfully submitted,



Paula K. Wittmayer
Attorney for Applicant(s)
Reg. No. 53,785

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
Tel.: (203) 791-6692
Fax: (203) 798-4408
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